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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/780,142	Applicant(s) MILLER ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9 and 32-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9 and 32-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-6, 8-9 and 32-49 are pending.

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claim 50 has been renumbered 49.

3. Applicant's election with traverse of Group I, Claims 1-9 and 32 (now claims 1- 6, 8-9, and 32-49) drawn to a method of treating unwanted choroidal neovasculature that read on the elected photosensitizer of lutetium texaphyrin or Lu-Tex, the elected anti-angiogenesis factor of angiostatin and the elected unwanted choroidal neovasculature of aged related macular degeneration filed 4/29/02, is acknowledged. The traversal is on the grounds that (1) all claims read on the elected anti-angiogenesis factor of angiostatin, and the elected photosensitizer of lutetium and the elected disorder such as aged related macular degeneration. (2) Applicant submit that Groups II and III are directed towards methods of treating unwanted choroidal neovasculature using, among other thing, a targeting moiety that binds integrin α-vβ. (3) A search for targeting moieties that bind integrin α-vβ would necessary include both species of integrin of Group II and Group III. However, it is noted that amended claim 1 is now drawn to a method of treating unwanted choroidal neovasculature using distinct products such as angiostatin, endostatin, a peptide containing a RGD tripeptide that binds α-vβ, an antibody that binds α-vβ integrin, a Cox-2 inhibitor, a molecule that binds VEGFR, a molecule that binds EGFR, a molecule that binds VEGF, a tyrosine kinase inhibitor, and a pigment epithelium derived growth factor. These peptides, inhibitors are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the methods of treating different diseases such as unwanted choroidal neovasculature, idiopathic disorders, and inflammatory diseases that differs with respect their etiology with different products such as peptide, antibody, receptor, growth factor, enzyme or kinase inhibitor) which differ with their respect to their structure, mode of action, process steps and endpoints. Therefore, they are

patentably distinct. Therefore, the requirement of Group I (now claims 1-6, 8-9, and 32-49) and Groups II-V is still deemed proper and is therefore made FINAL.

4. Claims 1-6, 8-9, and 32-49, drawn to a method of treating unwanted choroidal neovasculature that read on the elected species photosensitizer of lutetium texaphyrin or Lu-Tex, the elected anti-angiogenesis factor of angiostatin and the elected unwanted choroidal neovasculature of aged related macular degeneration are being acted upon in this Office Action.

5. The references cited on PTO 1449 filed 4/29/02 have been crossed out because none of the cited references have been submitted to the Office.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 8-9, and 32-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of potentiates the apoptotic effect of photosensitizer such as Lutetium Texaphyrin (Lu-Tex) on endothelial cells in vitro, **does not** reasonably provide enablement for (1) a method of treating unwanted choroidal neovasculature comprising endothelial cells in any mammal, the method comprising the steps of: (a) administering to the mammal *any* anti-angiogenesis factor such as angiostatin, endostatin, *any* peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor, in an amount efficient to permit an effective amount to localized in the choroidal neovasculature for treating *any* disorder such as age-related macular degeneration; (b) administering to the mammal an amount of *any* photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (2) the said method

wherein the anti-angiogenesis factor is administered to any mammal such as primate and human prior to administration of the photosensitizer; (3) the said method wherein the photosensitizer is lutetium texaphyrin, *any* benzoporphyrin, *any* benzoporphyrin derivative, *any* hematoporphyrin, or *any* hematoporphyrin derivative; (4) the said method wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (5) the said method wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of *any* anti-angiogenesis factor; (6) the said method wherein the method ameliorates the symptoms of *any* disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, *any* idiopathic disorders, choroiditis, choroidal rapture, overlying choroids nevi and *any* inflammatory disease; (7) a method of treating unwanted choroidal neovasculature comprising endothelial cells in *any* mammal, the method comprising the steps of: (a) administering to the mammal such as primate and human *any* anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to the mammal an amount of *any* photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (8) the said method wherein the anti-angiogenesis factor is the ones such as angiostatin, endostatin, *any* peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor; (9) the said method wherein the photosensitizer is *any* lutetium texaphyrin, any benzoporphyrin, *any* benzoporphyrin derivative, *any* hematoporphyrin or *any* hematoporphyrin derivative; (10) the said method wherein the said method wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of *any* anti-angiogenesis factor; (11) the said method wherein the method ameliorates the symptoms of *any* disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, *any* idiopathic disorders, choroiditis, choroidal rapture, overlying choroids nevi and any inflammatory disease; (12) A method of treating *any* unwanted choroidal neovasculature comprising endothelial

cells in *any* mammal, the method comprising the steps: (a) administering to *any* mammal such as primate and human *any* anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to said mammal after step (a) an amount of *any* photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (13) the said method wherein the photosensitizer is *any* lutetium texaphyrin, any derivative; (14) the said method wherein the anti-angiogenesis factor is the ones such as angiostatin, endostatin, *any* peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor; (15) the said method wherein occlusion of the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (16) the said method wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of *any* anti-angiogenesis factor; (17) the said method wherein the method ameliorates the symptoms of *any* disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, any idiopathic disorders, choroiditis, choroidal rapture, overlying choroids nevi and any inflammatory disease for treating age-related macular degeneration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex) used in photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* when compared to angiostatin or Lu-Tex alone (page 24). The effect of Lutetium Texaphyrin (Lu-Tex) on BRCE cells appears to be apoptosis by increases Caspase-3 (page 27). The combination of angiostatin and Lu-Tex/PDT on BRCE cells increases caspase-3 like activity more abruptly and more rapidly as compared to Lu-Tex/PDT alone (page 28). The specification on page 15 defines the term "anti-angiogenesis factor" is any molecule, protein, peptide, nucleic acid (ribose nucleic acid (RNA) or deoxyribose nucleic acid (DNA)), protein/peptide inhibitors peptidyl nucleic acid, organic compound, or inorganic compound, that reduces or inhibits the formation of new blood vessels in a mammal.

The specification does not teach how to effectively treat *any* disorder such as unwanted choroidal neovasculature associated with age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, *any* idiopathic disorders, choroiditis, choroidal rupture, overlying choroids nevi and any inflammatory diseases by administering *any* anti-angiogenesis factor and *any* photosensitizer mentioned above in any mammal. There is insufficient guidance as how to make any anti-angiogenic factor such as "molecule, protein, peptide, nucleic acid (ribose nucleic acid (RNA) or deoxyribose nucleic acid (DNA)), protein/peptide inhibitors peptidyl nucleic acid, organic compound, or inorganic compound", much less having the same function. The term "molecule, protein, peptide, nucleic acid (ribose nucleic acid (RNA) or deoxyribose nucleic acid (DNA)), protein/peptide inhibitors peptidyl nucleic acid, organic compound, or inorganic compound" have no structure associated with function. Further, the specification does not teach how to extrapolate data obtained from in vitro proliferation and apoptosis assays to the development of effective in vivo human therapeutic compositions as a method of treating any unwanted choroidal neovasculature, any inflammatory disorders, idiopathic disorders and age-related macular degeneration that differ with respect to etiology and treatment endpoints commensurate in scope with the claimed invention.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

A method of treating unwanted choroidal neovasculature using *any* molecule, *any* DNA, or *any* RNA in the absence of *in vivo* data is unpredictable for the following reasons: (1) the

stability and the expression level of the DNA molecule in a vector has not been demonstrated; (2) the potential for adverse host immune response to said DNA molecule has not been addressed; (3) the mode of administration or delivery of said DNA molecule have not been addressed; (4) the specificity of the vector to specific cell types and (5) the type of protective immune response has not been demonstrated using any molecule mentioned above.

Verma *et al* teach that the inherent difficulties of gene therapy is the inability to deliver genes efficiently to the right type of cell, obtaining sustained expression of the therapeutic protein and without triggering the host immune responses (See page 239, in particular).

Even if the anti-angiogenesis factor is limited to angiostatin and the photosensitizer is limited to lutetium texaphyrin, there are no in vivo working examples in the specification as filed demonstrating that the combination of angiostatin and lutetium texaphyrin is effective for treating any unwanted choroidal neovasculature associated with *any* idiopathic disorder, and *any* inflammatory disease, much less age-related macular degeneration. A method of treating any disease in the absence of in vivo data is unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Given the indefinite number of undisclosed anti-angiogenic factor and photosensitizer, it is unpredictable which undisclosed anti-angiogenic factor in combination with which undisclosed photosensitizer such as any amino acid derivative, any azo dye, any xanthene derivative, any chlorin, any tetrapyrrole derivative, or any phthalocyanine would be useful as a method for treating unwanted choroidal neovasculature associated with age-related macular degeneration, let alone any idiopathic disorders, and any inflammatory diseases.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-6, 8-9, and 32-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of treating unwanted choroidal neovasculature comprising endothelial cells in any mammal, the method comprising the steps of: (a) administering to the mammal *any* anti-angiogenesis factor such as angiostatin, endostatin, *any* peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor, in an amount efficient to permit an effective amount to localized in the choroidal neovasculature for treating *any* disorder such as age-related macular degeneration; (b) administering to the mammal an amount of *any* photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (2) the said method wherein the anti-angiogenesis factor is administered to any mammal such as primate and human prior to administration of the photosensitizer; (3) the said method wherein the photosensitizer is lutetium texaphyrin, *any* benzoporphyrin, *any* benzoporphyrin derivative, *any* hematoporphyrin, or *any* hematoporphyrin derivative; (4) the said method wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (5) the said method wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of *any* anti-angiogenesis factor; (6) the said method wherein the method ameliorates the symptoms of *any* disorder such as age-related macular degeneration, ocular

histoplasmosis syndrome, pathologic myopia, angioid streaks, *any* idiopathic disorders, choroiditis, choroidal rapture, overlying choroids nevi and *any* inflammatory disease; (7) a method of treating unwanted choroidal neovasculature comprising endothelial cells in *any* mammal, the method comprising the steps of: (a) administering to the mammal such as primate and human *any* anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to the mammal an amount of *any* photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (8) the said method wherein the anti-angiogenesis factor is the ones such as angiostatin, endostatin, *any* peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor; (9) the said method wherein the photosensitizer is *any* lutetium texaphyrin, any benzoporphyrin, *any* benzoporphyrin derivative, *any* hematoporphyrin or *any* hematoporphyrin derivative; (10) the said method wherein the said method wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of *any* anti-angiogenesis factor; (11) the said method wherein the method ameliorates the symptoms of *any* disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, *any* idiopathic disorders, choroiditis, choroidal rapture, overlying choroids nevi and any inflammatory disease; (12) A method of treating *any* unwanted choroidal neovasculature comprising endothelial cells in *any* mammal, the method comprising the steps: (a) administering to *any* mammal such as primate and human *any* anti-angiogenesis factor in an amount sufficient to permit an effective amount to localize in the choroidal neovasculature; (b) administering to said mammal after step (a) an amount of *any* photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature; and (c) irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature, wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (13) the said method wherein the photosensitizer is *any*

lutetium texaphyrin, any derivative; (14) the said method wherein the anti-angiogenesis factor is the ones such as angiostatin, endostatin, *any* peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor; (15) the said method wherein occlusion of the choroidal neovasculature resulting from steps (a), (b) and (c) is greater than that resulting only from steps (b) and (c); (16) the said method wherein the method more selectively occludes choroidal neovasculature relative to the same treatment lacking administration of *any* anti-angiogenesis factor; (17) the said method wherein the method ameliorates the symptoms of *any* disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streaks, any idiopathic disorders, choroiditis, choroidal rapture, overlying choroids nevi and any inflammatory disease for treating age-related macular degeneration.

The specification discloses only pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex)/photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro* when compared to angiostatin or Lu-Tex alone (page 24). The effect of Lutetium Texaphyrin (Lu-Tex) on BRCE cells appears to be apoptosis by increases Caspase-3 (page 27). The combination of angiostatin and Lu-Tex/PDT on BRCE cells increases caspase-3 like activity more abruptly and more rapidly as compared to Lu-Tex/PDT alone (page 28). The specification on page 15 defines the term "anti-angiogenesis factor" is any molecule, protein, peptide, nucleic acid (ribose nucleic acid (RNA) or deoxyribose nucleic acid (DNA)), protein/peptide inhibitors peptidyl nucleic acid, organic compound, or inorganic compound, that reduces or inhibits the formation of new blood vessels in a mammal.

With the exception of the specific method of pre-treating bovine retinal capillary endothelial (BRCE) cells with angiostatin (500ng/ml) potentiates the effect of Lutetium Texaphyrin (Lu-Tex)/photodynamic therapy by irradiated at 5, 10 or 20 J/cm^2 *in vitro*, there is insufficient written description about the structure associated with function of *any* anti-angiogenesis factor such as the ones recited in claims 1, 33, 36, 41, and 46 and *any* photosensitizer is *any* benzoporphyrin, *any* benzoporphyrin derivative, *any* hematoporphyrin, *any* hematoporphyrin derivative for a method of treating unwanted choroidal neovasculature or

ameliorates the symptoms of any disorder such as age-related macular degeneration, ocular histoplasmosis syndrome, pathologic myopia, angioid streak, *any* idiopathic disorders, choroiditis, choroidal rupture, overlying choroids nevi, and *any* inflammatory disease.

Further, Applicant discloses the use of only one specific anti-angiogenic factor such as angiostatin and one specific photosensitizer such as lutetium texaphyrin for in vitro method of inhibiting endothelial cells growth. Given the lack of a written description of *any* additional representative species of anti-angiogenesis factor such as any molecule, any DNA, any RNA, any organic molecule or any inorganic molecule of angiostatin, endostatin, any peptide containing a RGD tripeptide sequence that binds α-vβ3 integrin, *any* antibody that binds α-vβ3 integrin, *any* COX 2 inhibitor, *any* molecule that binds to *any* vascular endothelial growth factor receptor, *any* molecule that binds epidermal growth factor receptor, *any* molecule that binds *any* vascular endothelial growth factor, *any* tyrosine kinase inhibitor, and *any* pigment epithelium derived growth factor for a method of treating unwanted choroidal neovasculature, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-6, 8-9, and 32-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,162,242 (Dec 2000, PTO 892) in view of US Pat No 5,733,876 (March 1998, PTO 892).

The '242 patent teaches a method of treating unwanted choroidal neovasculature such as proliferation of new blood vessels in the subretinal area of the eyes associated with macular degeneration or neoplastic cells by administering an agent such as adenosine diphosphate (ADP) to enhance thrombus formation prior to administering to the mammal such as human an amount of various photosensitizer such as ethyletiopurpurin, protoporphyrin, aminolevulinic acid which is an amino-derivative, benzoporphyrin derivative, Lutex (Lutetium texaphyrin) which is a tetrapyrrode derivative (See column 5, lines 5-51, column 8, lines 59-60, claims 1, 13-18 of the '242 patent, in particular) and irradiating the choroidal neovasculature with a laser light such that the light absorbance wavelength is around 630 nm to 732 nm absorbed by the photosensitizer so as to occlude the choroidal neovasculature (See column 8, lines 48-60, in particular). The benefits of the reference method are (1) it selectively destroying the neovascular tissue while radiation-induced damage to normal tissues and vessels is minimized or prevented (See column 6, lines 25-28, in particular).

The claimed invention differs from the reference only that the method comprises administering to the mammal an anti-angiogenesis factor such as angiostatin.

The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the coagulation factor in the method of treating unwanted choroidal neovasculature by administering coagulation factor and photosensitizer as taught by the '242 patent for the anti-angiogenesis factor such as angiostatin as taught by the '876 patent for a method of treating unwanted choroidal neovasculature associated with macular degeneration by administering angiostatin and photosensitizer as taught by the '242 patent and

the '876 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '876 patent teaches angiostatin is useful for a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration and angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular). The '242 patent teaches photosensitizer in combination with coagulation factor are useful for treating unwanted choroidal neovasculature such as proliferation of new blood vessels in the subretinal area of the eyes associated with macular degeneration and the benefits of photodynamic therapy using photosensitizer is that it selectively destroyed the neovascular tissue while radiation-induced damage to normal tissues and vessels is minimized or prevented (See column 6, lines 25-28, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). The recitation of wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (B) and (c) is an obvious results of the combined references teachings.

12. Claims 1-6, 8-9, and 32-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,707,986 (Jan 1998, PTO 892) or US Pat No 6,270,749 B1 (Aug 2001, PTO 892) each in view of US Pat No 5,733,876 (March 1998, PTO 892).

The '986 patent teaches a method of treating unwanted choroidal neovasculature such as formation of new blood vessel in the eyes associated with age-related macular degeneration of a mammal such as living primates and human comprising administering to the mammal an amount of photosensitizer such as green porphyrins or benzoporphyrin derivatives (BPD) sufficient to permit an effective amount to localize in the choroidal neovasculature and irradiating the choroidal neovasculature with laser light such as 692 nm of light from argon/dye laser (See column 7, lines 39-42, claims 1-6 of '986 patent, in particular).

The '749 patent teaches the use of photosensitizer such as texaphyrin complex with a diamagnetic metal such as Lutetium which is a tetrapyrrode derivative (See Abstract, column 8, lines 5-17, in particular) for a method of treating age-related macular degeneration (See column 23, lines 6-11, in particular). The '749 patent teaches the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography. (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular).

The claimed invention differs from the references only that the method comprises administering to the mammal an anti-angiogenesis factor such as angiostatin.

The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include angiostatin as taught by the '876 patent for a method of treating unwanted choroidal neovasculature comprising administering to the mammal an anti-angiogenesis factor such as angiostatin and photosensitizer sufficient to permit an effective amount to localize in the choroidal neovasculature and irradiating the choroidal neovasculature with laser light such that the light is absorbed by the photosensitizer so as to occlude the choroidal neovasculature. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '876 patent teaches angiostatin is useful for a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration and angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular). The '986 patent teaches photosensitizer such as green porphyrins or benzoporphyrin derivatives (BPD) is

effective as a method of treating unwanted choroidal neovasculature associated with age-related macular degeneration of a mammal such as living primates and human (See column 7, lines 39-42, claims 1-6 of '986 patent, in particular). The '749 patent teaches photosensitizer such as Lutetium texaphyrin is effective as a method of treating unwanted choroidal neovasculature associated with age-related macular degeneration because the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). The recitation of wherein damage to the endothelial cells resulting from steps (a), (b) and (c) is greater than that resulting only from steps (B) and (c) is an obvious results of the combined references teachings.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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